PCT / SE 2004 / 000450

PRV

PATENT- OCH REGISTRERINGSVERKET
Patentavdelningen

REC'D 05 APR 2004
WIPO PCT

Intyg
Certificate

Härmed intygas att bifogade kopior överensstämmer med de handlingar som ursprungligen ingivits till Patent- och registreringsverket i nedannämnda ansökan.

Ansökan ingavs ursprungligen på engelska.

This is to certify that the annexed is a true copy of the documents as originally filed with the Patent- and Registration Office in connection with the following patent application.

The application was originally filed in English.

(71) *Sökande* *AstraZeneca AB, Södertälje SE*
Applicant (s)

(21) *Patentansökningsnummer* *0300850-5*
Patent application number

(86) *Ingivningsdatum* *2003-03-25*
Date of filing

Stockholm, 2004-03-26

För Patent- och registreringsverket
For the Patent- and Registration Office

Marita Öun

Marita Öun

Avgift
Fee

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

PATENT- OCH REGISTRERINGSVERKET
SWEDEN

Postadress/Adress
Box 5055
S-102 42 STOCKHOLM

Telefon/Phone
+46 8 782 25 00
Vx 08-782 25 00

Telex
17978
PATOREG S

Telefax
+46 8 666 02 86
08-666 02 86

CHEMICAL COMPOUNDS

The present invention concerns piperidine derivatives having pharmaceutical activity, to processes for preparing such derivatives, to pharmaceutical compositions comprising such derivatives and to the use of such derivatives as active therapeutic agents.

Pharmaceutically active piperidine derivatives are disclosed in WO99/38514, WO99/04794 and WO00/35877.

Histamine is a basic amine, 2-(4-imidazolyl)-ethylamine, and is formed from histidine by histidine decarboxylase. It is found in most tissues of the body, but is present in high concentrations in the lung, skin and in the gastrointestinal tract. At the cellular level inflammatory cells such as mast cells and basophils store large amounts of histamine. It is recognised that the degranulation of mast cells and basophils and the subsequent release of histamine is a fundamental mechanism responsible for the clinical manifestation of an allergic process. Histamine produces its actions by an effect on specific histamine G-protein coupled receptors, which are of three main types, H1, H2 and H3. Histamine H1 antagonists comprise the largest class of medications used in the treatment of patients with allergic disorders, especially rhinitis and urticaria. H1 antagonists are useful in controlling the allergic response by for example blocking the action of histamine on post-capillary venule smooth muscle, resulting in decreased vascular permeability, exudation and oedema. The antagonists also produce blockade of the actions of histamine on the H1 receptors on c-type nociceptive nerve fibres, resulting in decreased itching and sneezing.

Chemokines are chemotactic cytokines that are released by a wide variety of cells to attract macrophages, T cells, eosinophils, basophils and neutrophils to sites of inflammation and also play a rôle in the maturation of cells of the immune system. Chemokines play an important rôle in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. The chemokine superfamily can be divided into two main groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C, or α) and Cys-Cys (C-C, or β) families. These are distinguished on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues and sequence similarity.

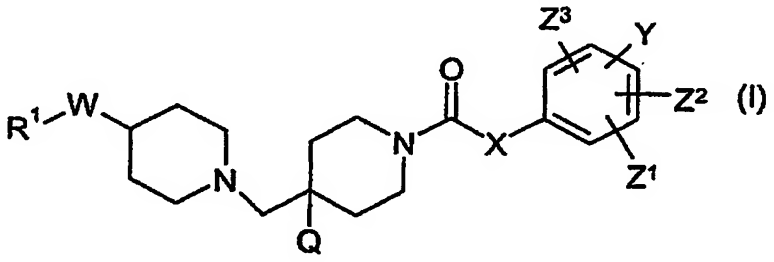
The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils such as human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β).

Studies have demonstrated that the actions of the chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3 and CXCR4. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

Viral infections are known to cause lung inflammation. It has been shown experimentally that the common cold increases mucosal output of eotaxin in the airways. Instillation of eotaxin into the nose can mimic some of the signs and symptoms of a common cold. (See, Greiff L *et al* Allergy (1999) 54(11) 1204-8 [Experimental common cold increase mucosal output of eotaxin in atopic individuals] and Kawaguchi M *et al* Int. Arch. Allergy Immunol. (2000) 122 S1 44 [Expression of eotaxin by normal airway epithelial cells after virus A infection].)

The present invention provides a compound of formula (I):



(I)

wherein:

Q is hydrogen or hydroxy;

W is CH_2, O or NR^2;

X is a bond, CH_2 or CH_2O;

Y is OH, CO_2R^3, SO_3H, $CH_2CO_2R^3$, CH_2SO_3H, $OCH_2CO_2R^3$ or OCH_2SO_3H;

Z^1, Z^2, Z^3 are, independently, hydrogen, halogen, cyano, nitro, hydroxy, NR^4R^5, C_{1-6} alkyl (optionally substituted with halogen), C_{1-6} alkoxy (optionally substituted with halogen), $S(O)_p(C_{1-6}$ alkyl), $S(O)_qCF_3$ or $S(O)_2NR^6R^7$;

R^1 is phenyl optionally substituted by halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or C_{1-4} haloalkoxy;

R^2 is hydrogen or C_{1-4} alkyl;

R^3 is hydrogen, C_{1-6} alkyl or benzyl;

p and q are, independently, 0, 1 or 2;

R^4, R^5, R^6 and R^7 are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-5}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^4 and R^5 below), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^4 and R^5 below), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^4 and R^5 below), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^4 and R^5 below), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);

alternatively NR^4R^5 or NR^6R^7 may, independently, form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, morpholine or piperazine, the latter optionally substituted by C_{1-4} alkyl on the distal nitrogen;

or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate thereof.

Certain compounds of the present invention can exist in different isomeric forms (such as enantiomers, diastereomers, geometric isomers or tautomers). The present invention covers all such isomers and mixtures thereof in all proportions.

Suitable salts include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulfonate or *p*-toluenesulfonate.

The compounds of the invention may exist as solvates (such as hydrates) and the present invention covers all such solvates.

Halogen includes fluorine, chlorine, bromine and iodine. Halogen is, for example, fluorine or chlorine.

Alkyl groups and moieties are straight or branched chain and comprise, for example, 1 to 6 (such as 1 to 4) carbon atoms. Examples of alkyl groups are methyl, ethyl, n-propyl, iso-propyl or tert-butyl.

Haloalkyl groups and moieties comprise an alkyl part, as defined above, and one or more (for example 1 to 6) of the same or different halogen atoms. Haloalkyl is, for example, CF_3.

Alkenyl groups comprise, for example, 2 to 6 (such as 2 to 4) carbon atoms. Examples of alkenyl groups are vinyl or allyl.

In one embodiment cycloalkyl groups comprise from 3 to 10 (such as 3 to 8, for example 3 to 6) carbon atoms and are mono-, bi or tricyclic. Cycloalkyl is, for example, cyclopropyl, cyclopentyl, cyclohexyl, norbornyl or camphoryl. The cycloalkyl ring is optionally fused to a benzene ring (for example forming a bicyclo[4.2.0]octa-1,3,5-trienyl or indanyl ring system). In a further embodiment cycloalkyl is monocyclic.

Heterocyclyl is an aromatic or non-aromatic 5 or 6 membered ring, optionally fused to one or more other rings, comprising at least one heteroatom selected from the group comprising nitrogen, oxygen and sulfur; or an N-oxide thereof, or an S-oxide or S-dioxide thereof. Heterocyclyl is, for example, furyl, thienyl (also known as thiophenyl), pyrrolyl, 2,5-dihydropyrrolyl, thiazolyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, piperidinyl, morpholinyl, pyridinyl, dihydropyridinyl (for example in a 6-oxo-1,6-dihydro-pyridinyl moiety), pyrimidinyl, indolyl, 2,3-dihydroindolyl, benzo[b]furyl (also known as benzfuryl), benz[b]thienyl (also known as benzthienyl or benzthiophenyl), 2,3-dihydrobenz[b]thienyl (for example in a 1-dioxo-2,3-dihydrobenz[b]thienyl moiety), indazolyl, benzimidazolyl, benztriazolyl, benzoxazolyl, benzthiazolyl (for example in a 1H-benzthiazol-2-one-yl moiety), 2,3-dihydrobenzthiazolyl (for example in a 2,3-dihydrobenzthiazol-2-one-yl moiety), 1,2,3-benzothiadiazolyl, an imidazopyridinyl (such as imidazo[1,2a]pyridinyl), thieno[3,2-b]pyridin-6-yl, 1,2,3-benzoxadiazolyl, benzo[1,2,3]thiadiazolyl, 2,1,3-benzothiadiazolyl, benzofurazan (also known as 2,1,3-benzoxadiazolyl), quinoxalinyl, dihydro-1-benzopyryliumyl (for example in a coumarinyl or a chromonyl moiety), 3,4-dihydro-1H-2,1-benzothiazinyl (for example in a 2-dioxo-3,4-dihydro-1H-2,1-

benzothiazinyl moiety), a pyrazolopyridine (for example 1H-pyrazolo[3,4-b]pyridinyl), a purine (for example in a 3,7-dihydro-purin-2,6-dione-8-yl moiety), quinolinyl, isoquinolinyl, dihydroisoquinolinyl (for example in a 2H-isoquinolin-1-one-yl moiety), a naphthyridinyl (for example [1,6]naphthyridinyl or [1,8]naphthyridinyl), a dihydro[1,8]naphthyridinyl (for example in a 1H-[1,8]naphthyridin-4-one-yl moiety), a benzothiazinyl, a dihydrobenzothiazinyl (for example in a 4H-benzo[1,4]thiazin-3-one-yl moiety), benzo[d]imidazo[2,1-b]thiazol-2-yl or dibenzothiophenyl (also known as dibenzothienyl); or an N-oxide thereof, or an S-oxide or S-dioxide thereof.

An N-oxide of a compound of formula (I) is, for example, a 1-oxy-[1,4']bipiperidinyl-1'-yl compound.

Heterocyclyl is, for example, pyrimidinyl or pyridinyl. In a further aspect of the invention heterocyclyl is optionally substituted by C_{1-4} alkyl or C_{1-4} alkoxy.

In one particular aspect the invention provides a compound of formula (I) wherein W is O.

In another aspect R^1 is phenyl optionally substituted (for example independently mono- or di-substituted) with halogen (for example chlorine or fluorine), C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy).

In a further aspect R^1 is phenyl optionally substituted (for example with one, two or three of the same or different) with fluorine, chlorine, C_{1-4} alkyl (for example methyl) or C_{1-4} alkoxy (for example methoxy). In a still further aspect R^1 is phenyl substituted by one, two or three (for example two or three) substituents independently selected from: fluorine, chlorine and methyl. For example R^1 is 3,4-dichlorophenyl, 2,4-dichloro-3-methylphenyl, 3,4-dichloro-2-methylphenyl, 2,4-dichlorophenyl, 4-chloro-2-methylphenyl or 2-chloro-4-fluorophenyl.

In a still further aspect of the invention Q is hydrogen.

In another aspect of the invention X is a bond.

In yet another aspect of the invention R^3 is hydrogen.

In a further aspect of the invention Y is CO_2H.

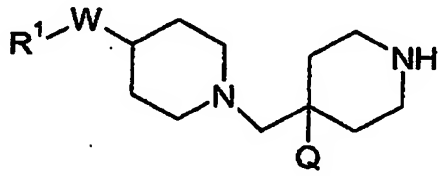
In a still further aspect of the invention Z^1, Z^2 and Z^3 are, independently, hydrogen, halogen, cyano, C_{1-4} alkyl (such as methyl or ethyl), C_{1-4} alkoxy (such as methoxy or ethoxy), CF_3, OCF_3, $S(O)_2(C_{1-4}$ alkyl) (such as $S(O)_2CH_3$) or $S(O)_2NH_2$.

In another aspect the present invention provides a compound of formula (I) wherein: Q is hydrogen; W is O; X is a bond; Y CO_2H; Z^1, Z^2 and Z^3 are, independently,

hydrogen, hydroxy or $S(O)_2(C_{1-4}$ alkyl) (for example $S(O)_2CH_3$); and R^1 is phenyl substituted by halogen (for example by one or two chlorine atoms) or C_{1-4} alkyl (for example methyl).

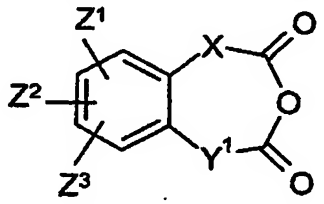
The compounds of the present invention can be prepared as described below.

A compound of formula (I), wherein Y is CO_2H, CH_2CO_2H or OCH_2CO_2H said Y group being ortho to the group X, can be prepared by acylating a compound of formula (II):



(II)

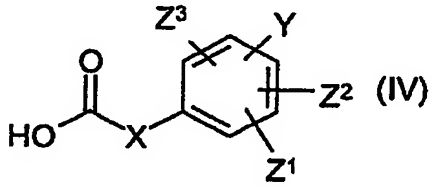
via the ring opening of an anhydride of formula (III):



(III)

wherein X is as defined above and Y^1 is a bond, CH_2 or OCH_2; in the presence of a suitable tertiary amine (such as triethylamine), in a suitable solvent (such as acetonitrile) at an elevated temperature (such as in the range 60-100°C).

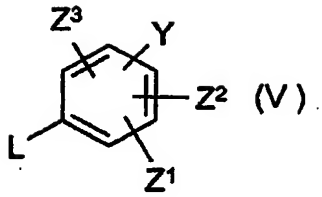
Alternatively, a compound of formula (I), wherein Y is CO_2R^3, $CH_2CO_2R^3$ or $OCH_2CO_2R^3$ and R^3 is not hydrogen, can be prepared by coupling a compound of formula (II) with a compound of formula (IV):



(IV)

either going via the acid chloride of the compound of formula (IV) (using standard techniques) or by using a coupling reagent (such as PyBrOP or HATU) under suitable conditions.

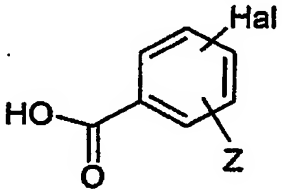
A compound of formula (I), wherein X is a bond and Y is CO_2R^3, can be prepared by carbonylation (such as palladium catalysed carbonylation) of a compound of formula (V):



(V)

wherein L is chloro, bromo, iodo or O-triflate, and then quenching the product so formed with a compound of formula (II).

A compound of formula (I), wherein X is a bond, Y is CO_2R^3, R^3 is not hydrogen, and R^1 does not have a chloro, bromo or iodo substituent, can also be made by coupling a compound of formula (II) with an acid of formula (VI):



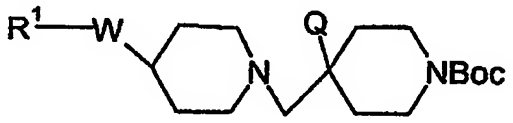
(VI)

wherein Hal is chloro, bromo or iodo, under the coupling conditions described above; then carbonylating the compound so formed (such as using a palladium catalysed carbonylation); and then quenching the product so formed with a C_{1-6} aliphatic alcohol or benzylalcohol.

For a compound of formula (I) where Y is or includes a CO_2R^3 group:

- when R^3 is hydrogen said compound may be converted to a compound of the invention where R^3 is not hydrogen by a standard esterification method well known in the art; and,
- when R^3 is not hydrogen said compound may be converted to a compound of the invention where R^3 is hydrogen by a standard ester hydrolysis method well known in the art.

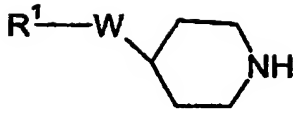
A compound of formula (II) can be prepared by deprotecting a compound of formula (VII):



(VII)

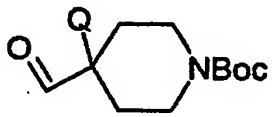
for example using trifluoroacetic acid in a suitable solvent (such as dichloromethane) or using a source of hydrogen chloride in a suitable solvent (such as dioxane).

A compound of formula (VII), wherein Q is hydrogen, can be prepared by reacting a compound of formula (VIII):



(VIII)

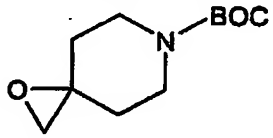
with a compound of formula (IX):



(IX)

in the presence of $NaBH(OAc)_3$ and acetic acid, in a suitable solvent (such as tetrahydrofuran or dichloromethane).

A compound of formula (VII), wherein Q is hydroxy, can be prepared by reacting a compound of formula (VIII) with a compound of formula (X):



(X)

in a suitable solvent (such as a C_{1-6} aliphatic alcohol, for example ethanol) at room temperature.

The preparation of various intermediates can be found in WO00/66559 and WO01/77101; alternatively they can be prepared by using or adapting literature methods.

Further compounds of formula (I) can be prepared by adaptation of: the routes described above, methods described in the art or the Examples recited below.

Compounds of formula (II) to (X) can be prepared by using or adapting methods described in the art. The preparation of various phenoxy piperidines is described in WO 01/77101.

In the above processes it may be desirable or necessary to protect an acid group or a hydroxy or other potentially reactive group. Suitable protecting groups and details of processes for adding and removing such groups may be found in "Protective Groups in Organic Synthesis", 3rd Edition (1999) by Greene and Wuts.

In another aspect the present invention provides processes for the preparation of compounds of formula (I).

The compounds of formula (I) have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR3) activity, and may be used in the treatment of autoimmune, inflammatory, proliferative or hyperproliferative diseases, or

immunologically-mediated diseases (including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)).

Examples of these conditions are:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behçet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, lichen planus, phemphigus, bullous phemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata, corneal ulcer or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome,

leprosy (such as lepromatous leprosy), peridontal disease, Sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle.

The compounds of formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof, are also H1 antagonists (and can, therefore, be used in the treatment of allergic disorders); and may also be used to control a sign and/or symptom of what is commonly referred to as a cold (for example a sign and/or symptom of a common cold or influenza or other associated respiratory virus infection).

According to a further feature of the present invention there is provided a method for treating a chemokine mediated disease state (especially a CCR3 mediated disease state) in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof.

According to another feature of the present invention there is provided a method for antagonising H1 in a mammal, such as man, suffering from, or at risk of, an H1 mediated disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof.

According to yet another feature of the present invention there is provided a method for treating a sign and/or symptom of what is commonly referred to as a cold in a mammal, such as man, suffering from, or at risk of, said disease state, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof.

The invention also provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof, for use in therapy.

In another aspect the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof, in the manufacture of a medicament for use in therapy (for example modulating chemokine receptor activity (especially CCR3 receptor activity), antagonising H1 or treating a sign and/or symptom of what is commonly referred to as a cold).

The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of:

(1) (the respiratory tract) obstructive diseases of airways including: chronic obstructive pulmonary disease (COPD) (such as irreversible COPD); asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; bronchitis {such as eosinophilic bronchitis}; acute, allergic, atrophic rhinitis or chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis; sarcoidosis; farmer's lung and related diseases; nasal polyposis; fibroid lung, idiopathic interstitial pneumonia, antitussive activity, treatment of chronic cough associated with inflammatory conditions of the airways or iatrogenic induced cough;

(2) (bone and joints) arthrides including rheumatic, infectious, autoimmune, seronegative spondyloarthropathies (such as ankylosing spondylitis, psoriatic arthritis or Reiter's disease), Behcet's disease, Sjogren's syndrome or systemic sclerosis;

(3) (skin and eyes) psoriasis, atopic dermatitis, contact dermatitis or other eczmatous dermitides, seborrhoetic dermatitis, lichen planus, phemphigus, bullous phemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides erythemas, cutaneous eosinophilias, uveitis, alopecia areata, corneal ulcer or vernal conjunctivitis;

(4) (gastrointestinal tract) Coeliac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, irritable bowel disease or food-related allergies which have effects remote from the gut (for example migraine, rhinitis or eczema);

(5) (Allograft rejection) acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea; or chronic graft versus host disease; and/or

(6) (other tissues or diseases) Alzheimer's disease, multiple sclerosis, atherosclerosis, Acquired Immunodeficiency Syndrome (AIDS), lupus disorders (such as lupus erythematosus or systemic lupus), erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome,

leprosy (such as lepromatous leprosy), Peridontal disease, sezary syndrome, idiopathic thrombocytopenia pupura or disorders of the menstrual cycle;

in a mammal (for example man).

In a further aspect the invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In a still further aspect a compound of formula (I), or a pharmaceutically acceptable salt thereof, is useful in the treatment of asthma.

The present invention also provides a the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of asthma {such as bronchial, allergic, intrinsic, extrinsic or dust asthma, particularly chronic or inveterate asthma (for example late asthma or airways hyper-responsiveness)}; or rhinitis {including acute, allergic, atrophic or chronic rhinitis, such as rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca or rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous or pseudomembranous rhinitis or scrofulous rhinitis; seasonal rhinitis including rhinitis nervosa (hay fever) or vasomotor rhinitis}.

In order to use a compound of the invention, or a pharmaceutically acceptable salt thereof or solvate thereof, for the therapeutic treatment of a mammal, such as man, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or a solvate thereof (active ingredient), and a pharmaceutically acceptable adjuvant, diluent or carrier.

In a further aspect the present invention provides a process for the preparation of said composition which comprises mixing active ingredient with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by

weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by topical (such as to the lung and/or airways or to the skin), oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art. A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 0.1mg and 1g of active ingredient.

Each patient may receive, for example, a dose of 0.01mgkg^{-1} to 100mgkg^{-1}, preferably in the range of 0.1mgkg^{-1} to 20mgkg^{-1}, of the active ingredient administered, for example, 1 to 4 times per day.

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) when given, ^{1}H NMR data is quoted and is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300MHz or 400MHz using perdeuterio DMSO-D6 (CD_3SOCD_3) or $CDCl_3$ as the solvent unless otherwise stated;

(ii) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI) or fast atom bombardment (FAB); where values for m/z are given, generally only ions which indicate the parent mass are reported, and unless otherwise stated the mass ion quoted is the positive mass ion - $(M+H)^+$;

(iii) the title and sub-title compounds of the examples and methods were named using the index name program from Advanced Chemistry Development Inc;

(iv) unless stated otherwise, reverse phase HPLC was conducted using a Symmetry™, NovaPak™ or Xerra™ reverse phase silica column; and

(v) the following abbreviations are used:

Boc or BOC	tert-butoxycarbonyl	DMSO	dimethylsulfoxide
HPLC	high pressure liquid chromatography	aq	aqueous

DIPEA	Diisopropylethylamine	RT	room temperature
RPHPLC	Reverse phase HPLC	TFA	Trifluoroacetic acid
HATU	O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluoro-phosphate		
PyBrOP	bromo-tris-pyrrolidinophosphonium hexafluorophosphate		

INTERMEDIATE 1

This process illustrates the preparation of 4-(3,4-dichlorophenoxy)-1-(4-piperidinylmethyl)-piperidine

a) 1,1-Dimethylethyl 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinecarboxylate

4-(3,4-Dichlorophenoxy)piperidine (1.27 g) was dissolved in tetrahydrofuran (20 mL); acetic acid (0.5 mL) and tert-butyl 4-formylpiperidine-1-carboxylate (1.43 g) were added to the solution. The reaction mixture was stirred at room temperature for 30 min then sodium triacetoxyborohydride (1.53 g) was added and the mixture was stirred at room temperature overnight. The reaction mixture was poured into 2M sodium hydroxide solution (50 mL) and product was extracted with diethyl ether. The combined ether extracts were washed with brine, dried, filtered and evaporated. Crude material was purified by flash chromatography, (eluting with 979:20:1 dichloromethane : methanol : aqueous ammonia) to give the sub-title compound (2.15 g).

MS 443/445 $[M+H]^+$ (ES+)

^{1}H NMR δ ($CDCl_3$) 1.06 (2H, ddd), 1.45 (9H, s), 1.61 - 1.82 (5H, m), 1.92 - 1.98 (2H, m), 2.16 - 2.27 (4H, m), 2.65 - 2.73 (4H, m), 4.08 (2H, d), 4.25 (1H, dq), 6.75 (1H, dd), 6.99 (1H, d), 7.30 (1H, d)

b) 4-(3,4-Dichlorophenoxy)-1-(4-piperidinylmethyl)-piperidine

1,1-Dimethylethyl 4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidine-1-carboxylate (1.0 g) was added to a mixture of 20% TFA in dichloromethane (20 mL) and the mixture was stirred at room temperature for 1 h. Solvent was removed by evaporation and 2M sodium hydroxide solution (25 mL) was added to the residue. The product was extracted with ethyl acetate and the organic phase was washed with brine, dried, filtered and evaporated to give the title compound (0.5 g).

MS 343/345 $[M+H]^+$ (ES+)

^{1}H NMR δ ($CDCl_3$) 1.10 (2H, qd), 1.60 (1H, qquintet), 1.73 - 1.83 (4H, m), 1.90 - 2.01 (2H, m), 2.16 - 2.26 (4H, m), 2.55 - 2.70 (4H, m), 3.09 (2H, d), 4.24 (1H, dquintet), 6.75 (1H, dd), 6.99 (1H, d), 7.27 (1H, d)

The following Intermediates were prepared analogously from the appropriate aryloxy piperidine:

Intermediate	Name (M+H)	^{1}H NMR δ ($CDCl_3$)
2	4-(2,4-Dichloro-3-methylphenoxy)-1-(4-piperidinylmethyl)-piperidine (357/359)	1.13 - 1.27 (2H, m), 1.57 - 1.70 (1H, m), 1.76 - 2.00 (2H, m), 2.16 - 2.32 (4H, m), 2.46 (3H, s), 2.60 - 2.99 (8H, m), 3.16 (2H, d), 4.31 (1H, quintet), 6.75 (1H, d), 7.18 (1H, d)
3	4-(4-Chloro-2-methylphenoxy)-1-(4-piperidinylmethyl)-piperidine (322/324)	1.08 - 1.21 (2H, m), 1.56 - 1.68 (1H, m), 1.73 - 1.86 (4H, m), 1.90 - 1.99 (2H, m), 2.16 - 2.31 (7H, m), 2.57 - 2.69 (4H, m), 3.12 (2H, d), 4.23 - 4.31 (1H, m), 6.74 (1H, d), 7.06 (1H, dd), 7.11 (1H, d)
4	4-(3,4-Dichloro-2-methylphenoxy)-1-(4-piperidinylmethyl)-piperidine (357/359)	(CD_3OD) 1.10 - 1.22 (2H, m), 1.66 - 1.85 (5H, m), 1.94 - 2.04 (2H, m), 2.22 (2H, d), 2.31 (3H, s), 2.32 - 2.41 (2H, m), 2.59 - 2.72 (4H, m), 3.08 (2H, d), 4.38 - 4.46 (1H, m), 6.91 (1H, d), 7.27 (1H, d)

EXAMPLE 1

This Example illustrates the preparation of 2-[[4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinyl]carbonyl]-benzoic acid.

4-{[4-(3,4-Dichlorophenoxy)piperidin-1-yl]methyl}piperidine (0.24 g), triethylamine (0.107 mL) and phthalic anhydride (0.109 g) were dissolved in acetonitrile (0.5 mL) and the reaction mixture was heated in a microwave oven at 80°C for 10 min. The solution was acidified to pH 4 by the addition of AcOH and was purified by RPHPLC

(5:95 MeCN:NH_4OAc (0.1% aq) gradient to 60:40 MeCN:NH_4OAc) to provide the title compound as a white solid (0.157 g)

MS $[M+H]^+$ (ES+) 491/493

^1H NMR δ (DMSO) 0.98 - 1.17 (2H, m), 1.49 - 1.67 (3H, m), 1.71 - 1.83 (2H, m), 1.85 - 1.97 (1H, m), 2.10 - 2.30 (4H, m), 2.60 - 2.75 (3H, m), 2.81 - 2.97 (2H, m), 3.15 - 3.27 (2H, m), 4.38 - 4.55 (2H, m), 6.97 (1H, dd), 7.22 - 7.27 (2H, m), 7.45 - 7.53 (2H, m), 7.60 (1H, td), 7.90 (1H, d)

The following Examples were prepared analogously to Example 1

Example	Name (M+H)	^1H NMR δ (CD_3OD)
2	2-[[4-[[4-(2,4-Dichloro-3-methylphenoxy)-1-piperidinyl]methyl]-1-piperidinyl]carbonyl]-benzoic acid (505/507)	1.17 - 1.29 (1H, m), 1.36 - 1.66 (2H, m), 1.91 - 2.19 (5H, m), 2.36 (3H, s), 2.71 - 2.99 (4H, m), 3.07 - 3.19 (4H, m), 3.26 - 3.37 (2H, m), 4.51 - 4.66 (2H, m), 6.91 (1H, d), 7.05 - 7.14 (1H, m), 7.19 (1H, d), 7.30 - 7.42 (2H, m), 7.87 (1H, d)
3	2-[[4-[[4-(3,4-Dichloro-2-methylphenoxy)-1-piperidinyl]methyl]-1-piperidinyl]carbonyl]-benzoic acid (505/507)	1.30 - 1.51 (2H, m), 1.59 - 1.71 (1H, m), 1.78 - 1.89 (4H, m), 1.98 - 2.08 (2H, m), 2.26 - 2.32 (2H, m), 2.34 (3H, s), 2.35 - 2.44 (2H, m), 2.67 - 2.76 (2H, m), 2.86 (1H, t), 3.03 (1H, t), 3.38 - 3.46 (1H, m), 4.41 - 4.50 (1H, m), 4.68 (1H, d), 6.94 (1H, d), 7.17 - 7.26 (1H, m), 7.31 (1H, d), 7.41 - 7.52 (2H, m), 7.94 (1H, d)

EXAMPLE 4

This Example illustrates the preparation of 2-[[4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinyl]carbonyl]-benzeneacetic acid

a) 2-[[4-[[4-(3,4-Dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinyl]carbonyl]-benzeneacetic acid methyl ester

To a stirred solution of 4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidine (0.24 g), 2-carboxy benzeneacetic acid methyl ester (0.143 g) and diisopropylethylamine (0.27 mL) in dichloromethane at RT was added PyBrOP (0.392 g).

The reaction was stirred for 16 h. The reaction mixture was diluted with 2 : 2 : 1 acetonitrile:methanol:water (5 mL) and acidified to pH 6 with acetic acid and subjected to purification using RPHPLC (25:75 MeCN:NH_4OAc (0.1% aq) gradient to 95:5 MeCN:NH_4OAc) to provide the sub-title compound as a white solid (0.220 g).

MS $[M+H]^+$ (ES+) 519/521

^1H NMR δ (CD_3OD) 1.01 - 1.18 (2H, m), 1.57 - 1.65 (1H, m), 1.66 - 1.76 (2H, m), 1.77 - 1.86 (2H, m), 1.89 - 1.98 (3H, m), 2.26 - 2.33 (2H, m), 2.39 (2H, t), 2.69 - 2.79 (2H, m), 2.83 - 3.07 (1H, m), 3.38 - 3.53 (2H, m), 3.57 (3H, s), 3.62 - 3.82 (1H, m), 4.31 - 4.38 (1H, m), 4.55 (1H, d), 6.80 (1H, dd), 7.01 (1H, d), 7.10 - 7.20 (1H, m), 7.22 - 7.34 (4H, m)

b) 2-[[4-[[4-(3,4-Dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinyl]carbonyl]-benzeneacetic acid

A solution of 2-[[4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-piperidinyl]carbonyl]-benzeneacetic acid methyl ester (0.188 g) and lithium hydroxide (0.046 g) in 3:1 methanol:water (2 mL) was stirred at RT for 16 h. The reaction mixture was acidified to pH 6 with acetic acid and subjected to purification using RPHPLC (5:95 MeCN:NH_4OAc (0.1% aq) gradient to 50:50 MeCN:NH_4OAc) to provide the title compound as a white solid (0.151 g).

MS $[M+H]^+$ (ES+) 505/507

^1H NMR δ (CD_3OD) 1.09 (1H, qd), 1.15 - 1.31 (2H, m), 1.60 - 1.80 (3H, m), 1.80 - 1.93 (2H, m), 1.94 - 2.02 (2H, m), 2.23 - 2.27 (1H, m), 2.27 - 2.36 (2H, m), 2.66 - 2.76 (2H, m), 2.79 - 2.92 (1H, m), 2.98 - 3.09 (1H, m), 3.33 - 3.45 (1H, m), 3.44 - 3.62 (2H, m), 4.34 - 4.41 (1H, m), 4.65 (1H, d), 6.88 (1H, dd), 7.07 (1H, d), 7.09 - 7.20 (1H, m), 7.21 - 7.29 (1H, m), 7.31 - 7.42 (3H, m)

EXAMPLE 5

This Example illustrates the preparation of 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-[4-hydroxy-3-(methylsulfonyl)benzoyl]-piperidine

a) 4-[[4-(3,4-Dichlorophenoxy)-1-piperidinyl]methyl]-1-[4-methoxy-3-(methylsulfonyl)benzoyl]-piperidine

To a stirred solution of 4-{[4-(3,4-dichlorophenoxy)piperidin-1-yl]methyl}piperidine (0.256 g), 4-methoxy-3-(methylsulfonyl)benzoic acid

(WO 98/41598; 0.18 g) and diisopropylethylamine (0.286 mL) in dichloromethane (3 mL) at RT was added PyBrOP (0.417 g). The reaction was stirred for 16 h. The reaction mixture was diluted with 1 : 1 acetonitrile/methanol (5 mL) and acidified to pH 6 with acetic acid and subjected to purification using RPHPLC (5:95 MeCN:NH_4OAc (0.1% aq) gradient to 95:5 MeCN:NH_4OAc) to provide the sub-title compound as a white solid (0.290 g).

MS $[M+H]^+$ (ES+) 555/557

^1H NMR δ (CD_3OD) 1.15 - 1.32 (2H, m), 1.78 - 1.91 (4H, m), 1.97 - 2.11 (3H, m), 2.50 (2H, d), 2.56 - 2.66 (2H, m), 2.87 - 2.95 (3H, m), 3.11 - 3.21 (1H, m), 3.25 (3H, s), 3.70 - 3.84 (1H, m), 4.06 (3H, s), 4.41 - 4.53 (1H, m), 4.50 - 4.67 (1H, m), 6.91 (1H, dd), 7.13 (1H, d), 7.35 (1H, d), 7.39 (1H, d), 7.75 (1H, dd), 7.95 (1H, d)

b) 4-[[4-(3,4-Dichlorophenoxy)-1-piperidinyl]methyl]-1-[4-hydroxy-3-(methylsulfonyl)benzoyl]-piperidine

The following reaction was performed in duplicate. A solution of 4-[[4-(3,4-dichlorophenoxy)-1-piperidinyl]methyl]-1-[4-methoxy-3-(methylsulfonyl)benzoyl]-piperidine (0.125 g) and sodium ethane thiolate (0.002 g) in DMF (4 mL) at RT was heated in a microwave oven at 150 °C for 25 min. The DMF was removed *in vacuo*, the residue was diluted with 1 : 1 acetonitrile/methanol (5 mL) and acidified to pH 6 with acetic acid. Purification using RPHPLC (5:95 MeCN:NH_4OAc (0.1% aq) gradient to 50:50 MeCN:NH_4OAc) provided the title compound as a white solid (0.014 g).

MS $[M+H]^+$ (ES+) 541/543

^1H NMR δ (CD_3OD) 1.06 - 1.21 (3H, m), 1.69 - 1.81 (4H, m), 1.87 - 2.01 (3H, m), 2.41 (2H, d), 2.47 - 2.56 (2H, m), 2.78 - 2.86 (3H, m), 2.88 - 3.11 (2H, m), 3.17 (3H, s), 4.35 - 4.42 (1H, m), 6.81 (1H, dd), 6.94 (1H, d), 7.03 (1H, d), 7.29 (1H, d), 7.48 (1H, dd), 7.77 (1H, d)

EXAMPLE 6

Pharmacological Analysis: Calcium flux $[Ca^{2+}]_i$ assay

Human eosinophils

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended ($5x10^6$ ml^{-1}) and loaded with 5μM FLUO-3/AM + Pluronic F127

2.2µl/ml (Molecular Probes) in low potassium solution (LKS; NaCl 118mM, $MgSO_4$ 0.8mM, glucose 5.5mM, Na_2CO_3 8.5mM, KCl 5mM, HEPES 20mM, $CaCl_2$ 1.8mM, BSA 0.1%, pH 7.4) for one hour at room temperature. After loading, cells were centrifuged at 200g for 5min and resuspended in LKS at $2.5x10^6$ ml^{-1}. The cells were then transferred to 96 well FLIPr plates (Poly-D-Lysine plates from Becton Dickinson pre-incubated with 5µM fibronectin for two hours) at 25µl/well. The plate was centrifuged at 200g for 5min and the cells were washed twice with LKS (200µl; room temperature).

A compound of the Examples was pre-dissolved in DMSO and added to a final concentration of 0.1%(v/v) DMSO. Assays were initiated by the addition of an A_{50} concentration of eotaxin and the transient increase in fluo-3 fluorescence (l_{Ex} =490nm and l_{Em} = 520nm) monitored using a FLIPR (Fluorometric Imaging Plate Reader, Molecular Devices, Sunnyvale, U.S.A.).

Compounds of the Examples were found to be antagonists if the increase in fluorescence induced by eotaxin (a selective CCR3 agonist) was inhibited in a concentration dependent manner. The concentration of antagonist required to inhibit the fluorescence by 50% can be used to determine the IC_{50} for the antagonist at the CCR3 receptor.

EXAMPLE 7

Human eosinophil chemotaxis

Human eosinophils were isolated from EDTA anticoagulated peripheral blood as previously described (Hansel et al., *J. Immunol. Methods*, 1991, 145, 105-110). The cells were resuspended at $10x10^6$ ml^{-1} in RPMI containing 200 IU/ml penicillin, 200 µg/ml streptomycin sulfate and supplemented with 10% HIFCS, at room temperature.

Eosinophils (700 µl) were pre-incubated for 15 mins at 37° C with 7 µl of either vehicle or compound (100x required final concentration in 10% DMSO). The chemotaxis plate (ChemoTx, 3µm pore, Neuroprobe) was loaded by adding 28µl of a concentration of eotaxin 0.1 to 100nM (a selective CCR3 agonist over this concentration range) containing a concentration of a compound according to the Examples or solvent to the lower wells of the chemotaxis plate. The filter was then placed over the wells and 25 µl of eosinophil suspension were added to the top of the filter. The plate was incubated for 1 hr at 37° C in a humidified incubator with a 95% air/5% CO_2 atmosphere to allow chemotaxis.

The medium, containing cells that had not migrated, was carefully aspirated from above the filter and discarded. The filter was washed once with phosphate buffered saline (PBS) containing 5 mM EDTA to remove any adherent cells. Cells that had migrated through the filter were pelleted by centrifugation (300xg for 5 mins at room temperature) and the filter removed and the supernatant transferred to each well of a 96-well plate (Costar). The pelleted cells were lysed by the addition of 28 µl of PBS containing 0.5% Triton x100 followed by two cycles of freeze/thawing. The cell lysate was then added to the supernatant. The number of eosinophils migrating was quantified according to the method of Strath et al., *J. Immunol. Methods*, 1985, 83, 209 by measuring eosinophil peroxidase activity in the supernatant.

Compounds of the Examples were found to be antagonists of eotaxin mediated human eosinophil chemotaxis if the concentration response to eotaxin was shifted to the right of the control curve. Measuring the concentration of eotaxin required to give 50% chemotaxis in the presence or absence of compounds enables the apparent affinity of the compounds at CCR3 to be calculated.

EXAMPLE 8

Guinea-pig isolated trachea

(See for example, Harrison, R.W.S., Carswell, H. & Young, J.M. (1984) European J. Pharmacol., 106, 405-409.)

Male albino Dunkin-Hartley guinea-pigs (250g) were killed by cervical dislocation and the whole trachea removed. After clearing the adherent connective tissue, the trachea was cut into six ring segments each three cartilage bands wide and then suspended in 20ml organ baths containing Krebs-Henseleit solution of the following composition (mM): NaCl 117.6, NaH_2PO_4 0.9, $NaHCO_3$ 25.0, $MgSO_4$ 1.2, KCl 5.4, $CaCl_2$ 2.6 and glucose 11.1. The buffer was maintained at 37°C and gassed with 5% CO_2 in oxygen. Indomethacin (2.8µM) was added to the Krebs solution to prevent development of smooth muscle tone due to the synthesis of cyclo-oxygenase products. The tracheal rings were suspended between two parallel tungsten wire hooks, one attached to an Ormed beam isometric force transducer and the other to a stationary support in the organ bath. Changes in isometric force were recorded on 2-channel Sekonic flat bed chart recorders.

Experimental protocols

At the beginning of each experiment a force of 1g was applied to the tissues and this was reinstated over a 60 minute equilibration period until a steady resting tone was achieved. Subsequently, a cumulative histamine concentration effect (E/[A]) curve was constructed at 0.5 $\log_{10}$ unit increments, in each tissue. The tissues were then washed and approximately 30 minutes later, test compound or vehicle (20% DMSO) was added. Following an incubation period of 60 minutes a second E/[A] curve was performed to histamine.

Contraction responses were recorded as a percentage of the first curve maximum.

Data analysis

Experimental E/[A] curve data were analysed for the purposes of estimating the potencies ($p[A_{50}]$ values) of histamine in the absence and presence of the test compound. Affinity (pA_2) values of test compounds were subsequently calculated using the following equation:

$$\log(r-1) = \log[B] + pA_2$$

where $r = [A]_{50}$ in presence of test compound/$[A]_{50}$ in absence of antagonist and [B] is the concentration of test compound. Compounds of the Examples were found to be H1 antagonists.

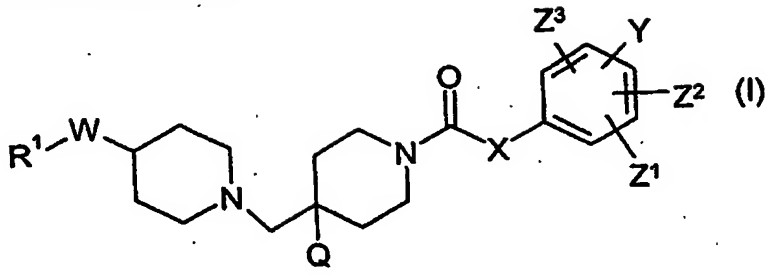
EXAMPLE 9

Histamine H1 receptor binding activity of compounds of the invention was assessed by competition displacement of 1nM [3H]-pyrilamine (Amersham, Bucks, Product code TRK 608, specific activity 30Ci/mmol) to 2µg membranes prepared from recombinant CHO-K1 cells expressing the human H1 receptor (Euroscreen SA, Brussels, Belgium, product code ES-390-M) in assay buffer (50mM Tris pH 7.4 containing 2mM $MgCl_2$, 250mM sucrose and 100mM NaCl) for 1 hour at room temperature.

Example	H1 pKi /[1328_S]
1	6.5
2	7.2
3	6.7
4	6.6
5	7.5

CLAIMS

1. A compound of formula (I):



wherein:

Q is hydrogen or hydroxy;

W is CH_2, O or NR^2;

X is a bond, CH_2 or CH_2O;

Y is OH, CO_2R^3, SO_3H, $CH_2CO_2R^3$, CH_2SO_3H, $OCH_2CO_2R^3$ or OCH_2SO_3H;

Z^1, Z^2, Z^3 are, independently, hydrogen, halogen, cyano, nitro, hydroxy, NR^4R^5, C_{1-6} alkyl (optionally substituted with halogen), C_{1-6} alkoxy (optionally substituted with halogen), $S(O)_p(C_{1-6}$ alkyl), $S(O)_qCF_3$ or $S(O)_2NR^6R^7$;

R^1 is phenyl optionally substituted by halogen, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy or C_{1-4} haloalkoxy;

R^2 is hydrogen or C_{1-4} alkyl;

R^3 is hydrogen, C_{1-6} alkyl or benzyl;

p and q are, independently, 0, 1 or 2;

R^4, R^5, R^6 and R^7 are, independently, hydrogen, C_{1-6} alkyl (optionally substituted by halogen, hydroxy or C_{3-10} cycloalkyl), $CH_2(C_{2-5}$ alkenyl), phenyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^4 and R^5 below), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^4 and R^5 below), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3) or heterocyclyl (itself optionally substituted by halogen, hydroxy, nitro, NH_2, $NH(C_{1-4}$ alkyl), $N(C_{1-4}$ alkyl)$_2$, $S(O)_2(C_{1-4}$ alkyl), $S(O)_2NH_2$, $S(O)_2NH(C_{1-4}$ alkyl), $S(O)_2N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as

described for R^4 and R^5 below), cyano, C_{1-4} alkyl, C_{1-4} alkoxy, $C(O)NH_2$, $C(O)NH(C_{1-4}$ alkyl), $C(O)N(C_{1-4}$ alkyl)$_2$ (and these alkyl groups may join to form a ring as described for R^4 and R^5 below), CO_2H, $CO_2(C_{1-4}$ alkyl), $NHC(O)(C_{1-4}$ alkyl), $NHS(O)_2(C_{1-4}$ alkyl), $C(O)(C_{1-4}$ alkyl), CF_3 or OCF_3);
alternatively NR^4R^5 or NR^6R^7 may, independently, form a 4-7 membered heterocyclic ring, azetidine, pyrrolidine, piperidine, azepine, morpholine or piperazine, the latter optionally substituted by C_{1-4} alkyl on the distal nitrogen;
or an N-oxide thereof; or a pharmaceutically acceptable salt thereof; or a solvate thereof.

2. A process for preparing a compound of formula (I) as claimed in claim 1.

3. A pharmaceutical composition which comprises a compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, and a pharmaceutically acceptable adjuvant, diluent or carrier.

4. A compound of the formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, for use in therapy.

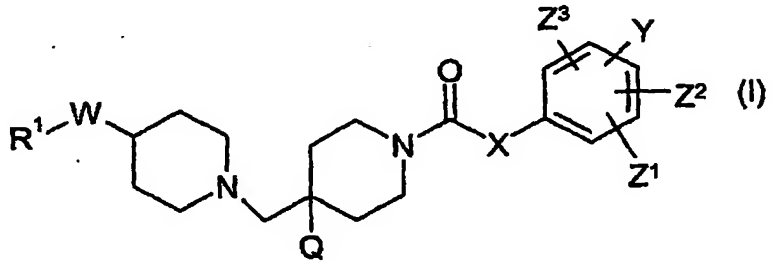
5. A compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1, in the manufacture of a medicament for use in therapy.

6. A method of treating a chemokine mediated disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof or solvate thereof as claimed in claim 1.

ABSTRACT

CHEMICAL COMPOUNDS

The present invention provides a compound of a formula (I):



(I)

wherein the variables are defined herein; to a process for preparing such a compound; and to the use of such a compound in the treatment of a chemokine (such as CCR3) or H1 mediated disease state.